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Original Article

Microsubthalamotomy improves sleep in patients affected by advanced Parkinson's disease

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ABSTRACT

Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) improves sleep in patients affected by Parkinson's disease (PD). Since microsubthalamotomy (mSTN) shows positive effects on motor symptoms, it could improve sleep in PD patients. Our goals were: to assess the effects of mSTN on sleep in patients affected by advanced PD; and to look for a correlation between sleep and motor features after the neurosurgical procedure.

Methods: Fifteen patients who underwent bilateral STN-DBS were enrolled. Subjective sleep evaluation was assessed using the Parkinson's Disease Sleep Scale (PDSS). Data on sleep schedule and presence of restless legs syndrome (RLS) were obtained. Objective sleep features were investigated by polysomnography (PSG). To evaluate the mSTN effect, we compared motor state and sleep features before and after the neurosurgical procedure, before the programmable pulse generator was switched on.

Results: mSTN had beneficial effects on motor state and sleep features. After the surgery, the mean total PDSS score increased from 84.0 ± 25.2 to 115.2 ± 16.6 ($P < 0.001$). PD patients reported longer total sleep time duration, decreased daytime sleepiness, and improvement in RLS symptoms. PSG data showed an increase in total sleep time and sleep efficiency with a decrease in wakefulness after sleep onset and arousal index. No correlation between motor improvements and sleep features modifications was observed after mSTN.

Conclusions: mSTN improves sleep quality and ameliorates several sleep complaints, as well as motor symptoms, in advanced PD patients who have undergone STN-DBS.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms, such as rest tremor, bradykinesia, rigidity and postural instability. However, in the last few years several studies have shown that PD also shows non-motor features [1]. In particular, sleep disturbances as well as neuropsychiatric symptoms (depression, cognitive dysfunctions, and psychosis) and dysautonomia affect many PD patients [2].

In a community-based study, sleep disturbances were reported in 60% of PD patients [3]. This prevalence increases during the course of the neurodegenerative disorder [4]. Insomnia, restless legs syndrome (RLS), periodic leg movements (PLM), REM (rapid eye movement) sleep behaviour disorder (RBD) and complaints related to PD, such as tremor or rigidity at night, impair sleep and contribute to causing excessive daytime sleepiness (EDS) [5].

Deep brain stimulation of the subthalamic nucleus (STN-DBS) has been shown to be a valuable treatment for motor symptoms and complications in advanced PD [6]. Furthermore, STN-DBS is effective in improving subjective and objective sleep features in PD patients [7–14]. Although mechanisms of sleep improvement after STN-DBS remain unknown, an increase in nocturnal mobility due to amelioration of motor symptoms could play a primary role [8].

In patients who have undergone STN-DBS, surgical tracks for intraoperative electrophysiological recordings and placement of the electrodes may cause a transient (days to weeks) improvement of parkinsonian signs and symptoms [15]. This effect, known as microsubthalamotomy (mSTN), is mainly due to traumatic tissue reactions and represents an immediate predictor of long-term STN stimulation efficacy [16,17]. Based on its positive effects on

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motor symptoms, mSTN should be able to improve sleep in patients affected by advanced PD who have undergone STN-DBS.

The aims of this study were: (1) to assess the effects of mSTN on subjective and objective sleep features in patients affected by advanced PD who have undergone STN-DBS; (2) to look for a correlation between sleep and motor features after the surgery.

2. Methods

2.1. Patients

From March 2011 to February 2012 we consecutively enrolled 15 patients (11 males and four women) with advanced PD (mean pre-surgical off-medication Hoehn and Yahr stage: 3.6 ± 0.6) who had undergone bilateral STN-DBS.

A diagnosis of idiopathic PD was made according to the UK Parkinson's Disease Society Brain Bank Criteria [18], and all patients fulfilled the criteria of the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease [19].

The mean disease duration was 10.6 ± 3.8 years. The pre-surgical levodopa equivalent dose was 1012.8 ± 342.2 mg.

Seven PD patients took psychotropic medications. In particular, they were treated using clonazepam 0.5 mg (two patients), lormetazepam 1.25 mg (one patient), zolpidem 10 mg (one patient), mirtazapine 15 mg (one patient), duloxetine 60 mg (one patient), and melatonin 5 mg (one patient). None took antipsychotics.

The local ethics committee approved the study. After receiving a detailed explanation of the protocol, all patients provided written informed consent.

2.2. Surgical procedure

The neurosurgical procedure has been described by Lettieri et al. in a previous paper [20]. In particular, microelectrode recordings were performed on three tracks on each side (anterior, central and posterior) for all the participating patients.

2.3. Study protocol

Subjective and objective sleep evaluations were carried out one week before (T1) and one week after the surgery (T2). The dosage of antiparkinsonian and psychotropic medications remained unchanged between T1 and T2. Assessments of motor state and sleep features were performed before the programmable pulse generator was switched on.

2.4. Motor evaluation

The pre- and post-surgical motor state was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) after a withdrawal of dopaminergic treatment (off medication) of $\geqslant$12 h.

2.5. Subjective sleep evaluation

Patients completed the Parkinson's Disease Sleep Scale (PDSS). PDSS is a visual analogue scale addressing 15 common symptoms associated with sleep disturbances in PD (Box 1). The severity of symptoms is reported by marking a cross along a 10 cm line. The scores for each question range from 0 (symptoms severe or experienced constantly) to 10 (no symptoms). The maximum PDSS score is 150 [21]. As an Italian version of this scale was not available at the time of the study, the English version was translated into Italian and then retranslated and compared with the original by two independent professional translators, blinded to the previous version.

Box 1 Parkinson's Disease Sleep Scale: questions

1. The overall quality of your night's sleep.
2. Do you have difficulty falling asleep each night?
3. Do you difficulty staying asleep?
4. Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?
5. Do you fidget in bed?
6. Do you suffer from distressing dreams at night?
7. Do you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?
8. Do you get up at night to pass urine?
9. Do you have incontinence of urine because you are unable to move due to 'off symptoms'?
10. Do you experience numbness or tingling of your arms or legs which wake you from sleep at night?
11. Do you have painful muscle cramps in your arms or legs whilst sleeping at night?
12. Do you wake early in the morning with painful posturing of arms or legs?
13. On waking do you experience tremor?
14. Do you feel tired and sleepy after waking in the morning?
15. Have you unexpectedly fallen asleep during the day?

Sleep schedule data (sleep latency and total sleep time [TST]) were obtained by means of a structured questionnaire. The Stanford Sleepiness Scale (SSS) was adopted to evaluate daytime sleepiness [22]. The SSS is a one-item, self-rating, seven-point Likert-type scale designed to assess subjective sleepiness. A high score indicates a high level of sleepiness. The SSS was completed at 09:00. Patients were instructed to compare pre- and post-surgical sleep features.

A neurologist certified as a sleep expert by the Italian Sleep Medicine Association investigated the presence of RLS and RBD. RLS was diagnosed according to the four clinical criteria proposed by the International Restless Legs Syndrome Study Group [23]. Clinical conditions mimicking RLS were excluded. The International Restless Legs Syndrome Rating Scale (IRLS) was used to assess RLS severity [24]. Since the evaluation was performed over a short time, only patients reporting RLS symptoms nightly were considered as RLS-affected. The International Classification of Sleep Disorders criteria were adopted to diagnose the presence of RBD [25].

2.6. Polysomnographic evaluation

The patients underwent in-laboratory polysomnography (PSG) on two consecutive nights both at T1 and T2. The first nights were considered to be adaptation nights and were not analyzed. The patients reported that the nights spent in the sleep laboratory were comparable with their habitual sleep at home.

Electroencephalogram (EEG) electrodes were set according to standard criteria, using frontal, central and occipital head electrodes with references at the mastoids. Frontal (F4–A1), central (C4–A1) and occipital (O2–A1) EEG recordings were obtained. An electro-oculogram, submental electromyography (EMG) and a tibial anterior EMG of both legs were carried out, and nasal and oral airflow, movements of the chest and abdomen, snoring, transcutaneous oxygen saturation and pulse rate were also measured and recorded.

Sleep stages were classified according to the American Academy of Sleep Medicine (AASM) criteria [26]. Arousal index (AI),

apnea–hypopnea index (AHI), and periodic leg movements during sleep index (PLMSI) were also calculated.

Presence of tonic EMG activity during REM was evaluated according to the method described by Gagnon et al. [27].

Recordings were assessed by a technician with experience in PSG performed in PD patients and masked regarding time of the neurophysiological evaluation. Artefacts due to surgery and electrode implantation were not observed.

2.7. Statistical analysis

Normal distribution was tested by means of the Kolmogorov–Smirnov test. Since our variables were normally distributed, the Student's *t*-test for paired samples was used to compare the continuous data at T1 and T2. Correlations between improvements in the motor score (UPDRS-III) and sleep parameters (total PDSS score; PDSS items 1, 3, 4, 5, 8, 9, 11, 12, 15; subjective total sleep time; SSS score; total sleep time; wake after sleep onset; arousal index; sleep efficiency) were evaluated by means of Spearman correlation coefficients. The data are given in tables as mean and standard deviation (SD), if not otherwise specified. $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using SPSS 17.0 software.

3. Results

3.1. Motor evaluation

The mean UPDRS-III score changed from 33.7 ± 9.0 at T1 to 21.9 ± 8.1 at T2 ($P < 0.001$). Compared with the pre-surgical period, the mean UPDRS-III improvement was 33% (range, 9–76).

3.2. Subjective sleep evaluation

Several PDSS domains significantly improved at T2 compared to T1 (Fig. 1). In particular, mSTN had beneficial effects on sleep quality (at T1, 4.6 ± 1.7 vs at T2, 6.6 ± 1.5, $P = 0.02$), maintenance insomnia (at T1, 3.6 ± 2.7 vs at T2, 6.9 ± 1.7, $P = 0.006$), nocturnal motor restlessness (item 4: at T1, 6.0 ± 3.8 vs at T2, 8.7 ± 2.1, $P = 0.008$; item 5: at T1, 5.8 ± 2.4 vs at T2, 7.7 ± 2.3, $P = 0.03$), nocturia (item 8: at T1, 3.2 ± 2.5 vs at T2, 5.1 ± 2.4, $P = 0.04$; item 9: at T1, 6.6 ± 3.8 vs at T2, 8.6 ± 1.9, $P = 0.04$), nocturnal muscle cramps (at T1, 5.2 ± 3.7 vs at T2, 9.0 ± 1.3, $P = 0.004$), early morning dystonia (at T1, 5.5 ± 2.5 vs at T2, 7.9 ± 2.7, $P = 0.02$), and EDS (at T1, 6.0 ± 3.3 vs at T2, 8.3 ± 1.8, $P = 0.007$). The mean total PDSS score significantly increased from 84.0 ± 25.2 at T1 to 115.2 ± 16.6 at T2 ($P < 0.001$).

Sleep latency did not differ between T1 and T2 (14.5 ± 16.1 vs 14.7 ± 14.7 min, $P = 0.9$). By contrast, PD patients reported longer TST (446.0 ± 72.5 vs 326.0 ± 100.7, $P < 0.001$) and decreased daytime sleepiness (2.2 ± 1.4 vs 3.33 ± 1.4, $P = 0.04$) at T2 than at T1.

At T1, four PD patients satisfied our criteria for RLS. These patients reported a mean duration of RLS symptoms of 75 min and had a mean IRLS score of 22.2. At T2, only one patient reported RLS occurrence, but he reported that distressing symptoms had significantly improved (RLS duration, at T1: 240 min vs at T2: 60 min; IRLS score, at T1: 29 vs at T2: 15). Five patients were diagnosed as affected by RBD before the surgery.

3.3. Polysomnographic evaluation

PSG findings are shown in Table 1. After the surgery, we observed a significant increase in TST and sleep efficiency. By contrast, wakefulness after sleep onset (WASO) and AI decreased at T2.

At T1 five patients had AHI > 5 that remained unchanged after the surgery (at T1, 32.0 ± 20.1 vs at T2, 30.1 ± 25.8, $P = 0.7$). Three patients, having no respiratory event at T1, have shown a few hypopneas after the surgery. Almost all the sample, including the four patients with RLS, had a PLMSI unchanged after the surgery. Only one subject had a PLMSI significantly increased at T2 (0.9 vs 23.3). The percentage of tonic EMG activity during REM did not differ before and after mSTN in the five patients with RBD. This sleep parameter slightly increased in two patients without RBD at T2.

3.4. Correlations between motor and sleep features

At T1 the UPDRS-III score was correlated with AI ($r = 0.66$, $P = 0.20$). After mSTN the statistical analysis showed no correlation

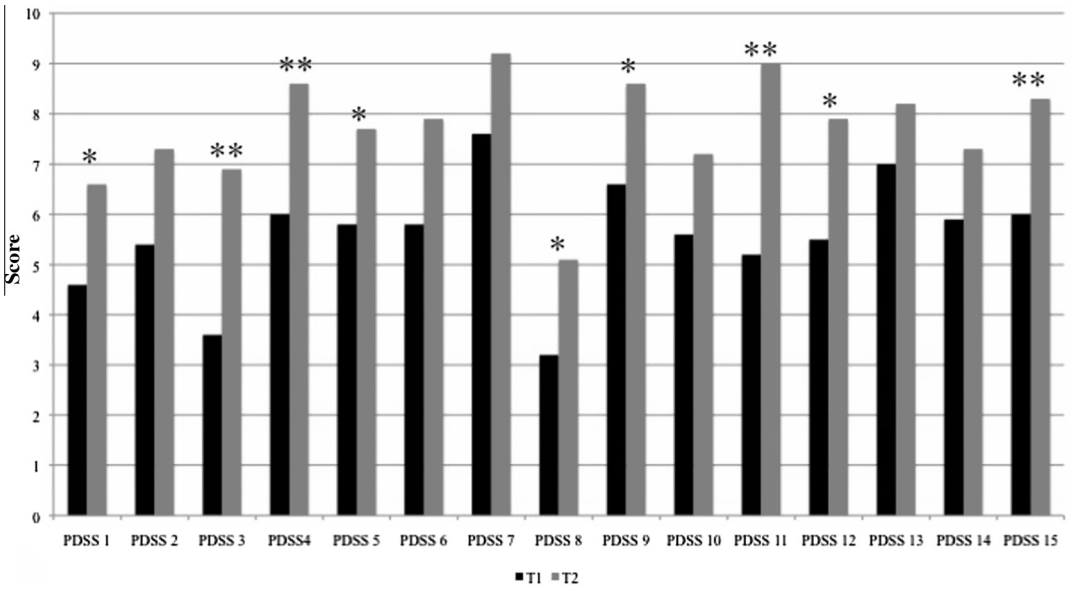

Fig. 1. The mean score for each of the 15 questions of the Parkinson's Disease Sleep Scale (PDSS). Sleep disturbances assessed by the PDSS items: (1) overall sleep quality; (2) sleep onset insomnia; (3) sleep maintenance insomnia; (4 and 5) nocturnal restlessness; (6 and 7) nocturnal psychosis; (8 and 9) nocturia; (10–13) nocturnal motor symptoms; (14) sleep refreshment; (15) daytime dozing. $^{*}P < 0.05$; $^{**}P < 0.01$. T1, before the neurosurgical procedure; T2, after the neurosurgical procedure. [Fig. 1. Please insert *y*-axis label: 'Score'. Please delete horizontal lines from graph area.]

Table 1
Polysomnographic findings before (T1) and after (T2) the neurosurgical procedure.

	T1	T2	*P*
Time in bed (min)	535.7 ± 81.5	558.5 ± 67.9	0.3
Total sleep time (min)	308.9 ± 72.2	364.7 ± 77.0	0.03
WASO (min)	212.9 ± 102.2	149.4 ± 90.3	0.03
Arousals (*n*)	34.5 ± 20.1	23.2 ± 13.0	0.08
Arousal index	19.7 ± 11.3	14.5 ± 8.2	0.05
Sleep efficiency (%)	58.9 ± 15.0	66.7 ± 12.3	0.04
REM latency (min)	105.0 ± 102.9	136.8 ± 104.6	0.4
N1 (%)	46.6 ± 28.7	47.2 ± 20.0	0.9
N2 (%)	43.4 ± 15.2	38.7 ± 16.4	0.3
N3 (%)	26.9 ± 15.5	34.4 ± 20.1	0.2
REM (%)	13.6 ± 11.5	13.3 ± 8.3	0.9
AHI	15.6 ± 19.1	15.9 ± 20.5	0.9
PLMSI	32.0 ± 50.2	39.0 ± 66.1	0.6
Tonic EMG during REM (%)	31.6 ± 27.2	25.3 ± 20.5	0.4

WASO, wake after sleep onset; REM, rapid eye movement sleep; AHI, apnea–hypopnea index; PLMSI, periodic leg movements during sleep index; EMG, electromyogram; N1, NREM stage 1; N2, NREM stage 2; N3, NREM stage 3.

between motor improvements and sleep features modifications (data not shown).

4. Discussion

Monaca et al. compared PSG data before and three months after STN-DBS, maintaining stimulation in the 'off' condition, in a sample of advanced PD patients. Since sleep parameters remained unchanged, the authors concluded that mSTN was not sufficient to improve sleep [10]. However, it should be borne in mind that: (1) only five patients were recorded with STN stimulation in the 'off' condition; (2) the mSTN effects are described only for a short period of time (days to weeks) after the surgery. Hence our study represents the first to investigate the mSTN effects on sleep in patients with advanced PD who have undergone STN-DBS.

Using the UPDRS-III score, Maltete et al. demonstrated that mSTN improved the total preoperative off-period motor score by 27% (range, 3–90) in a group of 30 patients affected by advanced PD [17]. We reproduced these data and observed a comparable improvement at the UPDRS-III.

In a further study Maltete et al. used a multiple stepwise regression analysis, reporting that the only predictor of a contralateral mSTN effect was the number of tracks used for microelectrode recordings. The authors concluded that tissue changes affecting both STN and its adjacent structures, such as the lenticular fasciculus and ansa lenticularis, might explain the mSTN effect on Parkinson's motor disability [16]. Since we performed the same number of tracks, three on each side, in our sample, we were unable to investigate this specific issue more exhaustively.

In 2002 Chauduri et al. developed the PDSS to screen for the presence of sleep disturbances in PD patients [21]. To date, three studies adopted this simple instrument to evaluate patient response to the effects of STN-DBS on sleep complaints in advanced PD patients. Although we investigated our patients before the programmable pulse generator was switched on, our results were in agreement with those of the previous surveys showing that the total PDSS score significantly increased after mSTN [11–13].

Our patients reported that sleep quality significantly improved after the surgical procedure. This beneficial effect of mSTN can be explained by a remarkable increase in TST observed at T2. Moreover, patients reported that sleep lasted longer and was more stable with fewer nocturnal awakenings after the surgery. These subjective experiences were confirmed by PSG data that demonstrated a significant increase in TST with a reduction in WASO and AI at T2. Similar objective features have been reported in patients affected by advanced PD who had undergone bilateral STN-DBS [7–10,12]. However, unlike previous studies investigating the effect of electrical impulses on sleep, we assessed, for the first time, whether an STN lesion influences features of sleep .

EDS affects many PD patients [28], and can sometimes cause sudden sleep attacks [29]. In these patients pathological somnolence presents as a multifactorial process in which the following determinants are involved: dopaminergic treatment, abnormal sleep architecture, and neurodegeration in sleep–wake regulation areas. Data on EDS in advanced PD patients after STN-DBS are partially conflicting. Contrary to findings by Hjort et al. [11], two recent studies showed that EDS significantly improves after the surgical procedure [12,13]. The authors hypothesized that this improvement could result from a reduction in dopaminergic treatment, improved sleep quality, and a direct effect of STN stimulation in the ascending activating network [12,13]. In our study mSTN improved daytime sleepiness (see the mean SSS score), reducing significantly the presence of pathological somnolence (see the mean score at the PDSS item 15). Since dopaminergic treatment was the same both before and after the surgery in our sample, we propose that EDS improved as a consequence of an improvement in sleep quality or due to the effects of mSTN on their own.

Little is known about RLS in PD patients who have undergone STN-DBS. Kedia et al. reported the new occurrence of RLS in 11 of 195 patients who were surgically treated. In particular, patients reporting RLS were treated with lower doses of dopaminergic drugs than those unaffected by the sleep disorder [30]. Postoperative cases of RLS did not occur in two further studies in which a significant improvement of the sleep disorder was documented [13,31]. Since the dosage of antiparkinsonian medication was the same before and after the surgery, we did not expect a new onset of RLS postoperatively in our sample. Nocturnal restlessness significantly improved (see the mean PDSS item 4 and 5 scores) and all four of the patients affected by daily RLS reported a notable amelioration of their distressing symptoms after mSTN (with three patients reporting no symptoms). It has been suggested that STN-DBS improves RLS as a consequence of changes in basal ganglia circuitry with downstream effects on the A11 dopaminergic area [13,31]. We hypothesize that mSTN mimics the effects of STN-DBS, thereby ameliorating RLS.

In our sample PLMSI did not decrease after mSTN. Similar results were reported by other authors after STN-DBS [7–9]. Interestingly, PLMSI remained unchanged also in the four patients referring an improvement of RLS symptoms after the surgery. Although a large proportion of RLS patients is affected by PLMS, these periodic movements can occur also without complaints of RLS. Wetter et al. observed a significantly higher PLMSI in PD patients not affected by RLS than in controls [32], and in a recent study prevalence of RLS did not differ between PD patients with and without PLMS [33]. Thus, it could be hypothesized that RLS and PLMS do not share a common pathophysiological mechanism in PD patients. Our results, showing a different effect of mSTN on RLS and PLMSI, are in agreement with this assumption.

Previous studies of advanced PD patients found that STN-DBS had no major effect on REM sleep without atonia [7–9]. We observed similar results after mSTN. Since we performed the study over a short period of time, the recurrence of RBD symptoms after the surgery in the five patients affected by this parasomnia could be considered.

Since (1) pre- and post-surgical pharmacological treatment remained unchanged, and (2) motor improvement was not correlated with sleep features modifications after the surgery, we hypothesize that mSTN has a direct effect on sleep physiology. STN is connected with anatomical structures, such as the pedunculopontine nucleus, dorsal raphe nucleus and laterodorsal tegmental nucleus, that are able to modulate behavioral status [34,35].

Some limitations should be acknowledged: (1) we evaluated a small sample of advanced PD patients. Thus, our results would need to be confirmed by further larger studies; (2) since assessment of some sleep complaints, such as nocturia and muscle cramps, was based only on a self-reported scale, the presence of a placebo effect cannot be excluded; (3) no validated scales to assess sleep quality were adopted; (4) the diagnostic criteria for RLS and the IRLS have not been validated in PD patients.

The strengths of this study were that: (1) sleep features and complaints were carefully investigated not only using subjective data, but also PSG data; (2) a physician with expertise in sleep disorders looked for the presence of specific complaints. Thus, we were able to exclude clinical conditions mimicking RLS that are very common in PD patients; (3) in contrast with previous studies performed in advanced PD patients who have undergone STN-DBS, our polysomnographic recordings were scored blindly.

For the first time, we showed that mSTN improves sleep quality and ameliorates several sleep complaints, as well as motor symptoms, in advanced PD patients who have undergone STN-DBS. Moreover, mSTN seems to affect these two clinical features independently. We think that this study could provide new insight into the mechanisms underlying the STN-DBS effects on sleep in PD patients.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.016.

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